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HEALTH EFFECTS ASSESSMENT FOR TRICHLOROETHYLENE

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16. ABSTRACT

This document represents a brief, quantitatively oriented scientific summary of health effects data. It was developed by the Environmental Criteria and Assessment Office to assist the Office of Emergency and Remedial Response in establishing chemical-specific health-related goals of remedial actions. If applicable, chemical-specific subchronic and chronic toxicity interim acceptable intakes are determined for systemic toxicants, or q_1^* values are determined for carcinogens for both oral and inhalation routes.

A q_1^* was determined for trichloroethylene based on both oral and inhalation exposure.

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PREFACE

This report summarizes and evaluates information relevant to a preliminary interim assessment of adverse health effects associated with trichloroethylene. All estimates of acceptable intakes and carcinogenic potency presented in this document should be considered as preliminary and reflect limited resources allocated to this project. Pertinent toxicologic and environmental data were located through on-line literature searches of the Chemical Abstracts, TOXLINE, CANCERLINE and the CHEMFATE/DATALOG data bases. The basic literature searched supporting this document is current up to September, 1984. Secondary sources of information have also been relied upon in the preparation of this report and represent large-scale health assessment efforts that entail extensive peer and Agency review. The following Office of Health and Environmental Assessment (OHEA) sources have been extensively utilized:

U.S. EPA. 1980b. Ambient Water Quality Criteria for Trichloroethylene. Environmental Criteria and Assessment Office, Cincinnati, OH. EPA 440/5-80-077. NTIS PB 81-117871.

U.S. EPA. 1981. The Carcinogen Assessment Group's Carcinogen Assessment of Trichloroethylene. OHEA, Washington, DC. Internal draft.

U.S. EPA. 1982. Hazard Profile for Trichloroethylene. Prepared by the Environmental Criteria and Assessment Office, Cincinnati, OH, OHEA for the office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1983a. Review of Toxicological Data in Support of Evaluation for Carcinogenic Potential of Trichloroethylene. Prepared by the Carcinogen Assessment Group, OHEA, Washington, DC for the Office of Solid Waste and Emergency Response, Washington, DC.

U.S. EPA. 1985. Health Assessment Document for Trichloroethylene. Environmental Criteria and Assessment Office, Research Triangle Park, NC, OHEA. EPA 600/8-82-006F. NTIS PB 84-162882.

The intent in these assessments is to suggest acceptable exposure levels whenever sufficient data were available. Values were not derived or larger uncertainty factors were employed when the variable data were limited in scope tending to generate conservative (i.e., protective) estimates. Nevertheless, the interim values presented reflect the relative degree of hazard associated with exposure or risk to the chemical(s) addressed.

Whenever possible, two categories of values have been estimated for systemic toxicants (toxicants for which cancer is not the endpoint of concern). The first, the AIS or acceptable intake subchronic, is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs during a limited time interval (i.e., for an interval that does not constitute a significant portion of the lifespan). This type of exposure estimate has not been extensively used or rigorously defined, as previous risk assessment efforts have been primarily directed towards exposures from toxicants in ambient air or water where lifetime exposure is assumed. Animal data used for AIS estimates generally include exposures with durations of 30-90 days. Subchronic human data are rarely available. Reported exposures are usually from chronic occupational exposure situations or from reports of acute accidental exposure.

The AIC, acceptable intake chronic, is similar in concept to the ADI (acceptable daily intake). It is an estimate of an exposure level that would not be expected to cause adverse effects when exposure occurs for a significant portion of the lifespan [see U.S. EPA (1980a) for a discussion of this concept]. The AIC is route specific and estimates acceptable exposure for a given route with the implicit assumption that exposure by other routes is insignificant.

Composite scores (CSs) for noncarcinogens have also been calculated where data permitted. These values are used for ranking reportable quantities; the methodology for their development is explained in U.S. EPA (1983b).

For compounds for which there is sufficient evidence of carcinogenicity, AIS and AIC values are not derived. For a discussion of risk assessment methodology for carcinogens refer to U.S. EPA (1980a). Since cancer is a process that is not characterized by a threshold, <u>any</u> exposure contributes an increment of risk. Consequently, derivation of AIS and AIC values would be inappropriate. For carcinogens, q_1^*s have been computed based on oral and inhalation data if available.

ABSTRACT

In order to place the risk assessment evaluation in proper context, refer to the preface of this document. The preface outlines limitations applicable to all documents of this series as well as the appropriate interpretation and use of the quantitative estimates presented.

Two oral bioassays have yielded positive results . In these studies, exposed mice showed an increased incidence of hepatocellular carcinoma. Using the geometric mean of the slope estimates from these studies, a carcinogenic potency of 1.1×10^{-2} $(mg/kg/day)^{-1}$ has been computed. Human epidemiological studies have not demonstrated a relationship between increased cancer risk and trichloroethylene exposure, nor has trichloroethylene been definitively shown to be carcinogenic in experimental animal species other than the mouse.

Trichloroethylene has been shown to be carcinogenic in mice by inhalation exposure in three separate experiments. Two of these studies have serious shortcomings. A positive response was not seen in inhalation cancer bioassays with rats and hamsters. U.S. EPA (1985) utilized the oral potency estimate and by applying appropriate pharmacokinetic conversions, estimated a unit risk of 1.3×10^{-6} $(\mu g/m^3)^{-1}$.

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LIST OF ABBREVIATIONS

ADI	Acceptable daily intake
AIC	Acceptable intake chronic
AIS	Acceptable intake subchronic
BCF	Bioconcentration factor
CAS	Chemical Abstract Service
CS	Composite score
LOAEL	Lowest-observed-adverse-effect level
NOAEL	No-observed-adverse-effect level
ppm	Parts per million
SNARL	Suggested no-adverse-response level
STEL	Short-term exposure limit
TLV	Threshold limit value
TWA	Time-weighted average

1. ENVIRONMENTAL CHEMISTRY AND FATE

The relevant physical and chemical properties and environmental fate of trichloroethylene (CAS No. 79-01-6) are as follows:

Chemical class:	halogenated aliphatic hydrocarbon (purgeable halocarbon)
Molecular weight:	131.5
Vapor pressure:	57.9 mm Hg at 20°C (Callahan et al., 1979)
Water solubility:	1100 mg/ℓ at 20°C (Callahan et al., 1979)
Octanol/water partition coefficient:	195 (Callahan et al., 1979)
Soil mobility: (predicted as retardation factor for soil depth of 140 cm and organic carbon content of 0.087%)	1.6 (Wilson et al., 1981)
BCF:	17 (in bluegill, Lepomis macrochirus) (U.S. EPA, 1980b)
Half-life in Air:	3.7 days (U.S. EPA, 1982)
Half-lives in Water:	1-4 days (river) (Zoeteman et al., 1980) 30-90 days (lake) (Zoeteman et al., 1980)

The half-life of trichloroethylene in soil could not be located in the literature searched. However, evaporation is expected to be the predominant loss mechanism from the soil surface. The half-life for soil evaporation should be longer than its evaporation half-life from water (Wilson et al., 1981). In subsurface soil, no significant degradation of trichloroethylene from soil is expected (Wilson et al., 1981). Therefore, significant amounts of trichloroethylene may leach into groundwater.

2. ABSORPTION FACTORS IN HUMAN AND EXPERIMENTAL ANIMALS

2.1. ORAL

Rats exhale 72-85% of ingested trichloroethylene through the lungs and excrete an additional 10-20% in the urine, indicating that at least 80-100% of ingested trichloroethylene is absorbed from the gastrointestinal tract (Daniel, 1963). Data are not available on the rate of absorption in humans.

2.2. INHALATION

Absorption of trichloroethylene through the lungs is rapid and reaches equilibrium in ~2 hours (U.S. EPA, 1980b).

3. TOXICITY IN HUMANS AND EXPERIMENTAL ANIMALS

3.1. SUBCHRONIC

3.1.1. Oral. Tucker et al. (1982) added trichloroethylene at four different dose levels to the drinking water of mice for 6 months (Table 3-1). The dose levels were calculated by measuring the concentration of trichloroethylene in the drinking water, and multiplying by the amount of water consumed by the animals each day. The amount of water consumed each day was estimated by measuring the water remaining in the drinking water bottles twice a week. Gas-liquid chromatography indicated that <20% of the trichloroethylene was lost from the drinking water solution in a 3- to 4-day period. It is not clear whether the authors included this loss of trichloroethylene with time in their calculations. However, using the dose levels that they report, the lowest dose level, 18.4 mg/kg/day in males and 17.9 mg/kg/day in females, produced no observed effects in the mice. The next dose level of 216.7 mg/kg/day in males and 193.0 mg/kg/day in females caused an increase in the ratio of liver weight to total body weight in males only. At a dose level of 393.0 mg/kg/day in males and 437.1 mg/kg/day in females, elevated ketone and protein levels appeared in the urine of males but not females, and the relative liver weight remained higher in males but was not increased in females. At the highest dose levels used in this experiment, 660.2 mg/kg/day for males and 793.3 mg/kg/day for females, both male and female mice had decreased body weights, increased liver and kidney weights, and increased levels of ketone and protein in the urine (Tucker et al., 1982).

3.1.2. Inhalation. In an earlier study, Adams et al. (1951) reported that exposure to trichloroethylene vapor 7 hours/day, 5 days/week for about 6 months decreased body weights in guinea pigs at a dose level of 200 ppm.

TABLE 3-1

Effects of Subchronic Trichloroethylene Exposure

Route	Dose/Exposure	Duration of Exposure	Species/Strain	Sex	Number Tested	Effect	Reference
Inhalation	control 35 ppm	NA continuous	rat/Long-Evans	NR NR	304 15	The only effect was depressed body weight in the three treated rabbits. No effects in any species were seen on survival, hematological values or gross or histological appearance of the internal organs.	Prendergast et al., 1967
	control 35 ppm	NA continuous	rabbit/ New Zealand	NR NR	48 3		
	35 ppm	continuous	guinea pigs/ Hartley	NR	15		
	35 ppm	continuous	squirrel monkey	NR	3		
	35 ppm	continuous	beagle dogs	NR	2		
Inhalation	control 55 ppm (300 mg/m³)	NA 8 hours/day, 5 days/week for 14 weeks	rats/SPF Wistar	M M	20 20	Increased liver weights observed in treated rats. No effects on hepatic or renal function, hematologic values, gross appearance of internal organs or behavior of animals. No histopathological evaluation presented.	Kimmerle and Eben, 1973
Oral, emulphor in water	control vehicle control 18.4 mg/kg/day 216.7 mg/kg/day 393.0 mg/kg/day 660.2 mg/kg/day	NA for 6 months	mice/CD-1	M	140 260 140 140 140 140	Body weights of males and females exposed to the highest dose were significantly lower. In males, liver weight (as a percentage of body weight) was increased at 216.7, 393.0 and 660.2 mg/kg/day; in females, increased liver weight was seen at a dose of 793.3 mg/kg/day. Increased kidney weights occurred in males exposed to 660.2 mg/kg/day and in females exposed to 793.3 mg/kg/day trichloroethylene. Elevated ketone and protein levels in urine were seen at the highest dose in both males and females, and at a dose of 393.0 mg/kg/day in males.	Tucker et al., 1982
	control vehicle control 17.9 mg/kg/day 193.0 mg/kg/day 437.1 mg/kg/day 793.3 mg/kg/day	NA for 6 months	mice/CD-1	F	140 260 140 140 140 140		

NA = Not applicable; NR = not reported

At a dose level of 400 ppm, rats had increased liver and kidney weights, and guinea pigs and rabbits had increased liver weights. Male rats and male guinea pigs had depressed body weights at a dose level of 400 ppm (Adams et al., 1951). Rats exposed to 55 ppm trichloroethylene vapor intermittently for 14 weeks (see Table 3-1) had increased liver weights, but no histopathology was reported. Hepatic and renal physiology, as well as clinical hematological values, appeared normal (Kimmerle and Eben, 1973). Prendergast et al. (1967) did not see any effects associated with continuous inhalation of 35 ppm trichloroethylene by rats, rabbits, guinea pigs, monkeys or dogs. Except for the rats, these authors used extremely small numbers of animals and only one dose level. Controls were described only for rats and rabbits.

3.2. CHRONIC

The available studies involving chronic trichloroethylene exposure (NCI, 1976; Bell et al., 1978; Maltoni, 1979; Henschler et al., 1980; Fukada et al., 1983) were designed to investigate the carcinogenicity of trichloroethylene. Therefore, a lack of reported noncancer-related toxic effects in these chronic studies may reflect a failure to look for them rather than their genuine absence.

3.2.1. Oral. In the NCI (1976) carcinogenicity bioassay, technical grade trichloroethylene was administered by gavage to rats and mice for 78 weeks. The rats had decreased body weights and survival times, as well as slight to moderate degenerative and regenerative alterations of renal tubules at both dose levels. However, the control rats also had a poor survival rate, so it is difficult to identify what, if any, results are treatment-related. The mice did not have decreased body weights or survival times after treatment with trichloroethylene. Although the incidence of hepatic adenoma, a presumably preneoplastic hepatic lesion, was reported, no other noncancerous histopathological changes were described (NCI, 1976).

3.2.2. Inhalation. Pertinent data regarding the chronic inhalation toxicity of trichloroethylene could not be located in the available literature.

3.3. TERATOGENICITY AND OTHER REPRODUCTIVE EFFECTS

3.3.1. Oral. Pertinent data regarding teratogenicity resulting from oral exposure to trichloroethylene could not be located in the available literature.

3.3.2. Inhalation. When Swiss-Webster mice and Sprague-Dawley rats were exposed to trichloroethylene vapor at a concentration of 300 ppm for 7 hours/day on days 6-15 of gestation (Schwetz et al., 1975), no treatment-related increase in malformations was seen. However, slightly reduced fetal body weight, delayed skeletal development and an increase in the incidence of undescended testes were observed in mice. Decreased maternal weight gain occurred in the rats.

When pregnant rabbits were exposed to trichloroethylene vapor at a concentration of 500 ppm for 7 hours/day, 5 days/week on days 6-21 of gestation, days 0-21 of gestation or beginning 3 weeks prior to mating and gestation, the offspring were reported to have an increased incidence of external hydrocephalus (Beliles et al., 1980). However, the U.S. EPA (1985) criticized the work because the authors failed to distinguish between true hydrocephalus externus and exencephaly associated with incomplete parietal ossification. Other, less definitive, teratogenicity studies include those of Taylor (1936), Bell (1977), Dorfmueller et al. (1981) and York et al. (1981). Generally, the only effects observed were reduced fetal body weight, body size and delayed ossification.

3.4. TOXICANT INTERACTIONS

Because trichloroethylene is bioactivated by liver microsomal enzymes, substances that stimulate liver microsomal enzymes will potentiate trichloroethylene toxicity, and substances that depress liver microsomal enzymes will decrease trichloroethylene toxicity. In addition, interactions with alcohol (Bardodej and Vyskoch, 1956; Seage and Burns, 1971; Cornish and Adefuin, 1966; Ferguson and Vernon, 1970; Gessner and Cabana, 1970) and carbon tetrachloride (Pessayre et al., 1982) enhance the toxicity of trichloroethylene. Trichloroethylene potentiates the effect of epinephrine on the myocardium (Dhumer et al., 1957; Defalque, 1961).

4. CARCINOGENICITY

4.1. HUMAN DATA

4.1.1. Oral. Although trichloroethylene has been reported to contaminate various human water supplies (Ziglio et al., 1983), pertinent data regarding carcinogenicity from oral exposure to trichloroethylene by humans could not be located in the available literature.

4.1.2. Inhalation. Three retrospective epidemiologic studies investigated human exposure to trichloroethylene in the workplace and subsequent tumor development (Axelson et al., 1978; Blair et al., 1979; Tola, 1978). Individuals in these studies were assigned to exposure categories on the basis of the amount of trichloroacetic acid, a trichloroethylene metabolite, in their urine or plasma. In the only study to find a significant increase in the incidence of cancer in exposed individuals (Blair et al., 1979), the workers had been exposed to tetrachloroethylene and carbon tetrachloride in conjunction with trichloroethylene. The relative amounts of each chemical during exposure were not determined. The other two studies (Axelson et al., 1978; Tola, 1978) did not find an increased incidence or rate of cancer development in individuals exposed to trichloroethylene.

4.2. BIOASSAYS

4.2.1. Oral. In the NCI (1976) study, mice and rats of both sexes were given trichloroethylene by gavage for 78 weeks. The mice were 5 weeks old at their first treatment; the rats were 7 weeks old. The mouse experiment was terminated after 90 weeks; the rat experiment, after 110 weeks. The doses listed in Table 4-1 are the TWA doses calculated for the 5 days/week that trichloroethylene was given to the rats and mice. In addition, the dose schedule was changed for both mice and rats during the course of the experiment. No treatment-related effects were seen in the rats, but high

TABLE 4-1

Carcinogenicity of Trichloroethylene

Route	Dose/Exposure	Duration of Treatment	Length of Experiment	Species/ Strain	Sex	Number Treated	Target Organ	Comments	Reference
Oral[a]	0 1169 mg/kg/day 2339 mg/kg/day	5 days/week for 78 weeks	90 weeks	mouse/ B6C3F1	M M M	20 50 48	liver	Hepatocellular tumors occurred in 26/50 (low-dose) and 31/48 (high-dose) of the treated males as compared with 1/20 control male mice ($p<0.05$ for both dose levels)	NCI, 1976
	0 869 mg/kg/day 1739 mg/kg/day	5 days/week for 78 weeks	90 weeks		F F F	20 50 47	liver	Hepatocellular tumors occurred in 4/50 (low-dose) and 11/47 (high-dose) of the treated females as compared with 0/20 control female mice ($p<0.05$ for the high-dose level only)	
	0 549 mg/kg/day 1097 mg/kg/day	5 days/week for 78 weeks	110 weeks	rat/ Osborne-Mendel	F/M F/M F/M	100/100 50/50 50/50	none	No effects were seen in rats.	
Oral[a]	untreated control vehicle control 500 mg/kg 1000 mg/kg	5 days/week, 103 weeks	103 weeks	rat/ Fisher 344	F/M	50/50 50/50 50/50 50/50	kidney	High-dose males showed significant increase in kidney adenocarcinomas.	NTP, 1982
Oral[a]	untreated control vehicle control 1000 mg/kg	5 days/week, 103 weeks	103 weeks	mouse/ B6C3F1	F/M	50/50 50/50 50/50	liver	Increased incidence of hepatocellular carcinoma in treated males and females.	NTP, 1982
Oral[b]	vehicle control 50 mg/kg 250 mg/kg	4-5 days/week for 52 weeks	140 weeks	rat/ Sprague-Dawley	F/M F/M F/M	30/30 30/30 30/30	none	No effect was observed on the health or mortality of any of the rats. Histological examination of the tissues revealed no pathological lesions.	Maltoni, 1979

TABLE 4-1 (cont.)

Route	Dose/Exposure	Duration of Treatment	Length of Experiment	Species/ Strain	Sex	Number Treated	Target Organ	Comments	Reference
Inhalation	0 100 ppm 300 ppm 600 ppm	6 hours/day, 5 days/week for 24 months	24 months	mouse/ B6C3F1	M M M M	99 95 100 97	liver	Hepatocellular carcinoma was reported in 28/95, 31/100 and 43/97 male mice exposed to 100, 300 and 600 ppm, respectively, of trichloroethylene. Controls had 18/99 mice with hepatocellular tumors ($p<0.05$ for comparison between treated and control mice)	Bell et al., 1978
	0 100 ppm 300 ppm 600 ppm	6 hours/day, 5 days/week for 24 months	24 months	mouse/ B6C3F1	F F F F	99 100 94 99	liver	Hepatocellular carcinoma was reported in 4/100, 9/94 and 13/99 female mice exposed to 100, 300 and 600 ppm, respectively, of trichloroethylene. Controls had 6/99 mice with hepatocellular tumors ($p<0.05$ for comparison between 600 ppm group and controls)	
	0 100 ppm 300 ppm 600 ppm	6 hours/day, 5 days/week for 24 months	24 months	rat/ Charles River	F/M F/M F/M	NA	none	No carcinogenic response.	
Inhalation	0 50 ppm 150 ppm 450 ppm	7 hours/day, 5 days/week for 104 weeks	107 weeks	mouse/ IRC	F F F F	49-50 49-50 49-50 49-50	lung	Mice exposed to 150 and 450 ppm trichloroethylene had 3 times the number of lung tumors observed in the low-dose animals and the controls.	Fukada et al., 1983
	0 ppm 50 ppm 150 ppm 450 ppm	7 hours/day, 5 days/week for 104 weeks	107 weeks	rat/SD	F F F F	49-51 49-51 49-51 49-51	none	A statistically significant increase was seen when the numberof lung adenocarcinomas in mice exposed to 150 and 450 ppm trichloroethylene was compared with the number of lung adenocarcinomas in the low-dose and control animals. It appears that trichloroethylene may promote the transformation of adenomas into adenocarcinomas. No carcinogenic effect in rats.	

TABLE 4-1 (cont.)

Route	Dose/Exposure	Duration of Treatment	Length of Experiment	Species/ Strain	Sex	Number Treated	Target Organ	Comments	Reference
Inhalation	0 ppm 100 ppm 500 ppm	6 hours/day, 5 days/week for 18 months	30 months	mouse/ Han:NMRI	F F F	29 30 28	lymphatic tissue	Histopathological examinations were made on all animals. No carcinogenic effect was observed in either sex of rats or hamsters, or in male mice. In female mice, the incidence of lymphomas was higher in the low-dose (17/30) and the high-dose (18/28) groups of animals than in the control (9/29) group.	Henschler et al., 1980
	0 ppm 100 ppm 500 ppm				M M M	30 30 30	none		
	0 ppm 100 ppm 500 ppm	6 hours/day, 5 days/week for 18 months	36 months	rat/ Wistar	F/M F/M F/M	30/30 30/30 30/30	none		
	0 ppm 100 ppm 500 ppm	6 hours/day, 5 days/week for 18 months	30 months	hamster/ Syrian	F/M F/M F/M	30/30 30/30 30/30	none		

[a]Vehicle was corn oil

[b]Vehicle was olive oil

NA = Not available

mortality rates within all groups of rats significantly detracted from the usefulness of the conclusions (U.S. EPA, 1982). There was a significant increase in the incidence of hepatocellular carcinomas in male mice at both dose levels. Females had a significantly increased incidence of hepatocellular carcinomas, but only at the high-dose level. The carcinogenic effect of trichloroethylene was greater in males than females. The rate of hepatocellular tumor development was dose-dependent, being greater in the male animals exposed to the high-dose level (NCI, 1976).

The National Toxicology Program (NTP, 1982) has recently completed a cancer bioassay using Fisher 344 rats. The trichloroethylene used had a purity >99.9% and epichlorohydrin was not detected in samples (detection level 0.001% v/v). Fifty male and 50 female rats were assigned to the following treatment groups: untreated control, vehicle control, 500 mg/kg trichloroethylene, 1000 mg/kg trichloroethylene. Trichloroethylene was administered in corn oil by gavage 5 days/week for 103 weeks.

A dose-related reduction in survival was noted in male rats. Both the low- and high-dose groups were significantly different from the vehicle control group using survival probabilities estimated by the Kaplan and Meier technique. High-dose males showed a significant ($p<0.05$) increase in kidney tubular adenocarcinomas (3/16) compared with vehicle controls (0/33) at terminal sacrifice by life table ($p=0.028$) and incidental tumor ($p=0.028$) tests. Tests for linear trend (Cochran-Armitage, Fisher Exact) were also significant. Historical control data showed a renal tumor incidence of 3/748 for this strain of rat. However, the comparison of kidney adenocarcinomas between high-dose males and vehicle controls did not show a significant difference using the Fisher Exact Test. Other treatment-related increases in tumor incidence were not documented.

Toxic nephrosis (cytomegaly) was found in 98 treated male rats and 100 treated female rats, but not in control rats. This lesion was found in rats dying during the course of the study.

The high dose used in this study appears to have exceeded the maximally tolerated dose as defined by NCI. Despite the increase in renal adenocarcinomas, NTP has concluded that this study is inadequate for a judgment on the carcinogenicity of trichloroethylene.

B6C3F1 mice were also tested in this study. A single dose of 1000 mg/kg/day 5 days/week for 103 weeks was used. Fifty males and 50 females were assigned to the untreated control, vehicle control and trichloroethylene groups. Body weights and survival were reduced in treated males when compared with vehicle controls. There was a significant ($p<0.002$) increase in incidence of hepatocellular carcinoma in treated male and female mice. Females showed incidences of 2/48 and 13/49 in the vehicle and treated groups, respectively. The corresponding incidences in males were 8/48 and 30/50. In addition, hepatocellular adenoma incidence was significantly ($p<0.05$) increased in female mice by the life table, incidental tumor and Cochran-Armitage and Fisher Exact tests, while in males significance was found only using life table analysis. Historical control data indicated hepatocellular tumor incidence of 18% and 2.9% for males and females, respectively. Cytomegaly of the kidney was found in 90% of the treated males and 98% of the treated females.

These results confirm those of the NCI (1976) study which reported increased incidence of hepatocellular carcinoma in male and female B6C3F1 mice given trichloroethylene stabilized with epoxides. These results indicate that the epoxides were not a requisite factor in the response.

Oral exposure to trichloroethylene at dose levels of 50 and 250 mg/kg for 1 year (see Table 4-1) produced no effects on Sprague-Dawley rats (Maltoni, 1979). The rats were 13 weeks old before trichloroethylene treatment began. As one part of a much larger experiment, Van Duuren et al. (1979) exposed 30 male and 30 female ICR/Ha Swiss mice to 0.5 mg trichloroethylene once a week for 622 days. No effects were reported.

4.2.2. Inhalation. Bell et al. (1978) reported the Manufacturing Chemists Association's audit findings on the bioassay conducted at Industrial Bio-Test Laboratories, Inc. from 1975-1977. In this study, mice and rats were exposed to 100, 300 or 600 ppm of trichloroethylene for 24 months (see Table 4-1). No carcinogenic effect was seen in rats. Hepatocellular carcinoma occurred in mice. In males, the incidence of hepatocellular carcinoma was greater at each dose level than in females and appeared at all dose levels tested. Hepatocellular carcinoma occurred at a significantly increased incidence in females only at the highest dose level. Several problems, including greatly vacillating exposure levels and replacement of animals during the experiment, challenge the validity of the results (U.S. EPA, 1982).

Female ICR mice and SD rats were exposed to 50, 150 and 450 ppm of trichloroethylene (Fukada et al., 1983) (see Table 4-1). Exposure began for both mice and rats at 7 weeks of age. No significant effects on body weight or mortality were produced by trichloroethylene. After 1 year of exposure, some animals developed bloody nasal discharge (rats), local alopecia (mice and rats), respiratory disorders (mice and rats) or a hunching appearance (mice), but the incidence and duration of these clinical observations were not discussed by the authors. Although hematopoietic and mammary tumors in mice and pituitary and mammary tumors in rats occurred frequently, the only

tumor type that occurred significantly more frequently in treated as compared with control animals was lung adenocarcinoma in mice. The development appeared dose-related and species-specific in that only 150 and 450 ppm trichloroethylene caused an increased incidence of pulmonary adenocarcinomas in mice only (Fukada et al., 1983).

After exposure to 100 and 500 ppm of trichloroethylene for 18 months, no effect on the body weights of rats, mice or hamsters was observed, and increased mortality was observed only in the mice (Henschler et al., 1980). For further experimental details, see Table 4-1. Age of the animals at the start of exposure was not disclosed. The only statistically significant effect ($p<0.05$) was an increased incidence and rate of development of malignant lymphomas in female mice. The response was greater, but apparently not significantly greater, in the high-dose than in the low-dose animals. The authors suggest that immunosuppression in the female mice is a contributing factor in the increased rate and incidence of the malignant lymphomas, but they provide no experimental basis for the suggestion. The control mice in the study (Henschler et al., 1980) had a higher incidence of lymphomas (30%) than the average (16%) reported by Luz (1977). In a preliminary report on a short-term study, Sanders et al. (1980) indicated that 14 days of 24 or 240 mg/kg of trichloroethylene by gavage decreased the immune response in male CD-1 mice.

4.2.3. Selected Pharmacokinetics Relevant to Dose-Response Estimates. A complete discussion of the pharmacokinetics of trichloroethylene is outside the scope of the present document. The pharmacokinetic data are extensively reviewed in U.S. EPA (1985). However, a brief summary of the data which relate to saturation kinetics is included here since these data form an integral part of dose estimates used for quantitative risk assessment for trichloroethylene. This discussion is excerpted from U.S. EPA (1985).

Experimental data indicate that the magnitude of trichloroethylene metabolism is dose-dependent in rodents showing saturation kinetics in both the mouse and rat at high dose levels. The dose required for saturation appears to be ~2000 mg/kg in mice and between 500 and 1000 mg/kg in rats. The maximal metabolic capacities in these species appear to be related to body surface area (U.S. EPA, 1985).

Experimental evidence indicates that metabolic pathways for trichloroethylene are qualitatively similar among mice, rats and humans (U.S. EPA, 1985).

The studies relating to trichloroethylene metabolism considered most relevant to interspecies dose-response extrapolation, as selected by U.S. EPA (1985), are summarized in the following paragraphs.

Prout et al. (1984) administered ^{14}C-trichloroethylene in corn oil as single intragastric doses of 10, 500, 1000 and 2000 mg/kg to male Osborne-Mendel and Wistar-derived rats and to male B6C3F1 and Swiss mice. Exhaled breath, urine, feces and carcass were analyzed for radioactivity and unmetabolized trichloroethylene for up to 72 hours after dosing. The results of these studies, as re-expressed by U.S. EPA (1985), are shown in Table 4-2.

The conclusions drawn from this study by U.S. EPA (1985) were as follows:

1. Virtually complete gastrointestinal absorption of trichloroethylene occurred for all doses in mice and rats.
2. No intraspecies strain differences were apparent.
3. Saturation of metabolism in the mouse began to occur at a dose of 1000 mg/kg based on excretion of unmetabolized trichloroethylene in the expired air.
4. Saturation of metabolism in rats began to occur at 500 mg/kg as indicated by exhalation of unchanged trichloroethylene at this dose level.

TABLE 4-2

Disposition of ^{14}C-TCI 72 Hours After Single Oral Doses to Male Osborne-Mendel and Wistar-Derived Rats and to Male B6C3F1 and Swiss Mice[a]

Dose (mg/kg)	Mice (mean of 4)			Dose (mg/kg)	Rats (mean of 4)		
	Dose/ Animal[b] (mg)	Metabolized (mg equivalent)	Exhaled (mg equivalent)		Dose/ Animal[b] (mg)	Metabolized (mg equivalent)	Exhaled (mg equivalent)
10	0.30	0.28	0.01	10	2.0	1.93	0.03
500	15.0	13.73	0.90	500	100.0	55.40	42.70
1000	30.0	23.28	5.25	1000	200.0	79.00	112.40
2000	60.0	46.90	8.16	2000	400.0	80.40	311.20

[a]Source: U.S. EPA, 1985

[b]Based on experimental weight of animals: rats, average 200 g; mice, 30 g.

For each of the dose levels U.S. EPA (1985) estimated the ratio of metabolized trichloroethylene in the rat to metabolized trichloroethylene in the mouse as follows:

Dose (mg/kg)	Ratio: Rat/Mouse (mg metabolized/animal)
10	(1.93/0.28) = 6.89
500	(55.4/13.73) = 4.03
1000	(79.0/23.28) = 3.39
2000	(80.4/46.9) = 1.71

U.S. EPA (1985) concluded from these data that for this dose range the fractional metabolism of trichloroethylene is more consistent with a $W^{2/3}$ dose estimate than a mg/kg ($W^{1.0}$) dose estimate.

Green and Prout (1984) orally dosed rats and mice for 180 days with 1000 mg/kg/day trichloroethylene in corn oil. Metabolism was evaluated by quantifying urinary metabolites (TCA and TCE-glucuronide). These data, as presented in U.S. EPA (1985), are shown in Table 4-3. The fractional metabolism appeared to be constant across time although the ratio of TCA to TCE-glucuronide increased. These data indicated that trichloro- ethylene did not accumulate significantly with repeated daily dosing.

DeKant et al. (1984), using balance studies, compared the metabolism of trichloroethylene in female Wistar rats and female NMRI mice. A single gavage dose of 200 mg/kg ^{14}C-trichloroethylene was administered to each animal. Radioactivity was measured in urine, feces, carcass and exhaled air for 72 hours postadministration. Virtually complete oral absorption was apparent. Data are shown in Table 4-4. The amount of trichloroethylene metabolized by rats and mice, as estimated by U.S. EPA (1985), is also shown in Table 4-4. Based on these data, U.S. EPA (1985) estimated a ratio of metabolized trichloroethylene as 5.05 for rat:mouse. This ratio agrees well with the estimated surface area ratio for the two species [$(240/24.4)^{0.67}$ = 4.46].

TABLE 4-3

Metabolism of TCI in B6C3F1 Mice: Effect of Chronic Dosing[a]
(1000 mg/kg/day)[b]

Day	Metabolized (mg equivalent)	Expired Unchanged (mg equivalent)
	Chronic	
1	18.27	5.28
10	22.50	4.08
180	15.75	7.11
	Single-dose Controls	
1	18.27	5.28
10	19.35	4.62
180	16.86	3.75

[a]Source: U.S. EPA, 1985

[b]Based on experimental weight of mice averaging 30 g, the daily dose per mouse equals 30 mg in 0.5 corn oil.

TABLE 4-4

Disposition of ^{14}C-TCI Radioactivity for 72 Hours After Single Oral Dose (200 mg/kg) to Rats and Mice (NMRI)[a]

	Mice (average of 3)[b]	Rats (average of 2)[b]
	Absolute dose 5.1 mg/animal	Absolute dose 48 mg/animal
	mg equivalent per animal	mg equivalent per animal
Expired TCI		
Unchanged	0.56 (11.0%)	24.96 (52.0%)
Metabolized		
$^{14}CO_2$	0.31	0.91
Urine	3.89	19.78
Feces	0.25	0.86
Carcass	0.10	1.39
Washes	0.01	0.10
	4.56 (89.4%)	23.04 (48.0%)
Total	5.12	48.0

[a]Source: U.S. EPA, 1985

[b]Based on experimental weight of animals: female rats, 140 g; female mice, 25.5 g.

Buben and O'Flaherty (1985) examined trichloroethylene metabolism in male Swiss-Cox mice administered trichloroethylene by gavage 5 days/week for 6 weeks. Doses used were 0, 100, 200, 400, 800, 1600, 2400 and 3200 mg/kg/day. Metabolism was evaluated by monitoring urinary metabolites. These data showed a linear relationship between urinary metabolites and for doses in the range of 0-1600 mg/kg trichloroethylene. At higher doses, saturation of metabolism is indicated by an abrupt plateau.

4.3. OTHER RELEVANT DATA

Trichloroethylene is often contaminated with carbon tetrachloride, chloroform, epoxides and other chemicals (Henschler et al., 1977; Loprieno et al., 1979), some of which are mutagenic. In order to eliminate the mutagenicity caused by contaminants, purified trichloroethylene has been tested. Purified trichloroethylene caused increased mutagenesis in Salmonella typhimurium (Bartsch et al., 1979; Baden et al., 1979; Simmon et al., 1977), and in Saccharomyces cerevisiae, strains D4 and D7 (Bronzetti et al., 1978) only after metabolic activation (U.S. EPA, 1981). Abrahamson and Valencia (1980) reported negative results in testing for sex-linked recessive lethal mutations in Drosophila melanogaster. Trichloroethylene did not induce dominant lethal mutations in NMRI-Han/BGA mice (Slacik-Erben et al., 1980). However, the result of mutagenicity testing in the mouse spot test was positive (Fahrig, 1977).

4.4. WEIGHT OF EVIDENCE

Inhalation of trichloroethylene has caused pulmonary adenocarcinomas (Fukada et al., 1983) and lymphomas (Henschler et al., 1980) in female mice, and hepatocellular carcinomas in both male and female mice (Bell et al., 1978). Oral exposure to trichloroethylene has caused hepatocellular carcinomas in both male and female mice (NCI, 1976). This appears to constitute

sufficient evidence of carcinogenicity in animals since carcinogenicity has been demonstrated for multiple strains of mice exposed by inhalation or gavage treatment. The evidence for carcinogenicity in humans appears to be inadequate. Applying the criteria proposed by the Carcinogen Assessment Group of the U.S. EPA for evaluating the overall weight of evidence for carcinogenicity (Federal Register, 1984), trichloroethylene is most appropriately classified a Group B2 - Probable Human Carcinogen.

5. REGULATORY STANDARDS AND CRITERIA

The ACGIH (1983) recommends a TWA-TLV of 50 ppm (270 mg/m^3) and an STEL of 150 ppm (560 mg/m^3) for trichloroethylene.

6. RISK ASSESSMENT

6.1. ACCEPTABLE INTAKE SUBCHRONIC (AIS)

Trichloroethylene is a chemical demonstrated to be a carcinogen, and data are sufficient for estimation of carcinogenic potencies by both the oral and inhalation routes. It is inappropriate, therefore, to calculate an AIS for this chemical.

6.2. ACCEPTABLE INTAKE CHRONIC (AIC)

Trichloroethylene is a chemical demonstrated to be a carcinogen, and data are sufficient for estimation of carcinogenic potencies by both the oral and inhalation routes. It is inappropriate, therefore, to calculate an AIC for this chemical.

6.3. CARCINOGENIC POTENCY (q_1*)

6.3.1. Oral. U.S. EPA (1985) has estimated the 95% upper-bound estimates for hepatocellular carcinoma using the linearized multistage model of Crump and adopted by the U.S. EPA (1980a) for the data from both the NCI (1976) and NTP (1982) studies. These data are shown in Table 6-1 which is adapted from U.S. EPA (1985).

Metabolized doses (see Table 6-1) were calculated from dose administered to rodents based on the data from Prout et al. (1984) using a "Michaeles-Menton" type equation, M = a X d/b+d): d represents the experimental dose, M represents the metabolized dose and a and b are empirically determined constants. Using least-square estimates, a was determined to be 594.1 and b 702.79 (r^2=0.99) (U.S. EPA, 1985). Using the multistage model, q_1* values were determined from animal metabolized doses. The q_1*s in terms of human metabolized doses were estimated from the animal q_1*s in terms of metabolized dose using a surface area approximation. Human q_1*s in terms of exposure dosage were then back-calculated from the q_1*s in terms of human metabolized doses (Table 6-2) (U.S. EPA, 1985).

TABLE 6-1

Incidence Rates of Hepatocellular Carcinomas in Male and Female Mice in the NTP (1982) and NCI (1976) Gavage Studies. Continuous Human Equivalent Dosages and Estimates of q_1^*, 95% Upper-Limit Slope, from the Linearized Multistage Model[a]

Study	Continuous Human Equivalent (animal nominal) Doses (mg/kg/day)[b]	Animal Metabolized Dose (mg/day)	Incidence Rates No. with Tumor/Total (%)
		MALE	
NTP	0 (0)	0	8/48 (17%)
	47.39[b] (1000)	31.98[c]	30/50 (60%)
NCI	0 (0)	0	1/20 (5%)
	45.11 (1169)[d]	30.90[c]	26/50 (52%)
	85.80 (2339)[d]	58.77[c]	31/48 (65%)
		FEMALE	
NTP	0 (0)	0	2/48 (4%)
	45.62 (1000)	28.17[c]	13/49 (27%)
NCI	0 (0)	0	0/20 (0%)
	31.65 (869)[d]	18.49[c]	4/50 (8%)
	61.43 (1739)[d]	35.89[c]	11/47 (23%)

[a]Source: Adapted from U.S. EPA, 1985

[b]All 95% upper-limit slopes q_1^* calculated using continuous human equivalent doses.

Equivalent human dosage = animal metabolized dose x 5/7 days x l_e/L_e $(W_a/70)^{1/3}$

where W_a = weight of the mice. The average weight of males is taken as 40 g for dosed males and 35 g for dosed females for the NTP study; for the NCI study the average weights are 33 g for males and 26 g for females. L_e, the length of experiment, = 2 years and l_e, the duration of exposure, is 2 years for the NTP study and 1.5 years for the NCI study.

[c]Determined using data from Prout et al. (1984) and a "Michaeles-Menton" type equation by U.S. EPA (1985)

[d]Time-weighted average gavage dose over 78-week treatment period.

TABLE 6-2

Estimated Slope Values (q_1^*) Based on Extrapolation from Data on Male and Female Mice[a,b]

Study	q_1^* (animal) (mg metabolized dose/kg/day)$^{-1}$	q_1^* (human) (mg metabolized dose/kg/day)$^{-1}$	q_1^* (human) (mg administered dose/kg/day)$^{-1}$
NTP			
male mice	1.8×10^{-3}	2.2×10^{-2}	1.9×10^{-2}
female mice	7.5×10^{-4}	9.5×10^{-3}	8.0×10^{-3}
NCI			
male mice	1.6×10^{-3}[c]	2.1×10^{-2}	1.8×10^{-2}
female mice	5.0×10^{-4}[c]	6.9×10^{-3}	5.8×10^{-3}
Geometric mean	1.0×10^{-3}	1.3×10^{-2}	1.1×10^{-2}

[a]Source: Adapted from U.S. EPA, 1985

[b]q_1^* is the 95% upper limit of the linear component (slope) in the multistage model. Since the dose-response curve is virtually linear below 1 mg/kg/day, the slope is numerically equal to the upper limit of the incremental lifetime risk estimates at 1 mg/kg/day.

[c]Slope is increased by $(104/90)^3$ due to the duration of the experiment being less than the lifespan of the test animal.

The potency for humans, q_1^*, to be used for estimates of risk related to exposure was estimated as the geometric mean of the human administered dose q_1^*s, 1.1×10^{-2} $(mg/kg/day)^{-1}$.

6.3.2. Inhalation. U.S. EPA (1985) estimated a unit risk for trichloroethylene in air of 1.3×10^{-6} $(\mu g/m^3)^{-1}$. This value is based on extrapolation from the human q_1^* of 1.3×10^{-2} (mg metabolized dose/kg/day)$^{-1}$ which was based on the geometric mean of values derived from the NTP and NCI oral bioassays. The oral q_1^* was converted to an inhalation unit risk based on human pharmacokinetic data.

The study by Monster et al. (1976) was used for estimating the amount metabolized when a subject is exposed to 1 $\mu g/m^3$ of TCI in air. The study presents the total uptake and the percentage excreted as TCI in the exhaled air for four subjects who were exposed to 70 and 140 ppm for 4 hours, including two half-hour 100-watt exercises. Since results from 70 and 140 ppm are comparable, the results for the 70 ppm group are used for risk calculation. These results are as follows:

Subject	Uptake (mg)	Percentage of Dose Exhaled as TCI	Total Dose Metabolized (mg)
A	500	9	455.0
B	450	17	373.5
C	470	10	423.0
D	660	8	607.2

The median amount metabolized by the four subjects is 439 mg. Assuming that the dose metabolized is linearly related to the level and duration of exposure, the dose corresponding to 1 $\mu g/m^3$ of trichloroethylene in air was estimated as:

$$\text{dose/1 } \mu g/m^3 \cong \frac{439 \text{ mg} \times (24 \text{ hours}/4 \text{ hours})}{70 \text{ ppm} \times 5475 \ \mu g/m^3/\text{ppm}}$$

$$= 6.9 \times 10^{-3} \ (mg/day)(\mu g/m^3)^{-1}$$

$$= 6.9 \times 10^{-3}/70 \text{ kg} = 9.9 \times 10^{-5} \ (mg/kg/day)^{-1}$$

Therefore, the unit risk for trichloroethylene in air is 1.3×10^{-2} (mg metabolized trichloroethylene/kg/day)$^{-1}$ x 9.9×10^{-5} (mg metabolized trichloroethylene/kg/day/$\mu g/m^3$) = 1.3×10^{-6} ($\mu g/m^3$)$^{-1}$.

Assuming a human 24-hour ventilatory volume of 20 m^3 and a body weight of 70 kg, the unit risk may be converted to 4.6×10^{-3} (mg/kg/day)$^{-1}$. U.S. EPA (1985) did not evaluate the data of Fukada et al. (1983) in the context of developing a unit risk for inhalation exposure to trichloroethylene. The Carcinogen Assessment Group is currently evaluating this study and its potential implications for the unit risk presented in U.S. EPA (1985).

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APPENDIX

Summary Table for Trichloroethylene

Carcinogenic Potency	Species	Experimental Dose/Exposure	Effect	q_1^*	Reference
Inhalation	mouse	1169-2339 mg/kg/day	hepatocellular carcinoma	4.6×10^{-3} $(mg/kg/day)^{-1}$	NCI, 1976; NTP, 1982; U.S. EPA, 1985
Oral	mouse	1169-2339 mg/kg/day	hepatocellular carcinoma	1.1×10^{-2} $(mg/kg/day)^{-1}$	NCI, 1976; NTP, 1982; U.S. EPA, 1985